

LEUCOSIS (LEUKAEMIA) IN CHILDHOOD

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Leucosis (Leukaemia) in Childhood.

Leucosis was first described by Hughes Bennett of Edinburgh in 1845. He described the enlarged spleen and called attention to the large number of leucocytes in the blood. He named the condition leukocythaemia. In the same year Virchow described this disease and called it leukaemia. He differentiated between a splenic leukaemia in which the principle pathological change was in the spleen and a lymphatic leukaemia in which the lymph glands were primarily involved. In 1857 Von Friedrich described the first case of acute leucosis. In 1891 Ehrlich published his work on differential stains for granular and non-granular leucocytes and made it possible to separate cases where the cells are mainly granular or myeloid from cases where the cells are chiefly non-granular or lymphocytes. Further progress has been made since then and the differentiation is more accurate so that we are now able to recognize what is known as monocytic leucosis.

Knowledge of leucosis in children and infants is of relatively recent origin. According to Adler, from the discovery of leucosis in 1845 until 1914 only seventeen cases in infants were reported and of these ten have been accepted. Ramsay in 1927 published an analysis of one hundred cases of leucosis in children, ninety one from the literature and nine from hospital records in Glasgow. Two years later Warren presented a review of the literature on acute leucosis. His conclusions were based on one hundred and thirteen cases on which autopsies had been performed, eighty five from the literature and twenty eight new cases. Of these one hundred and thirteen cases twenty seven were under the age of ten years. Since that time the literature has been increasing steadily but in the British periodicals

CHART 1

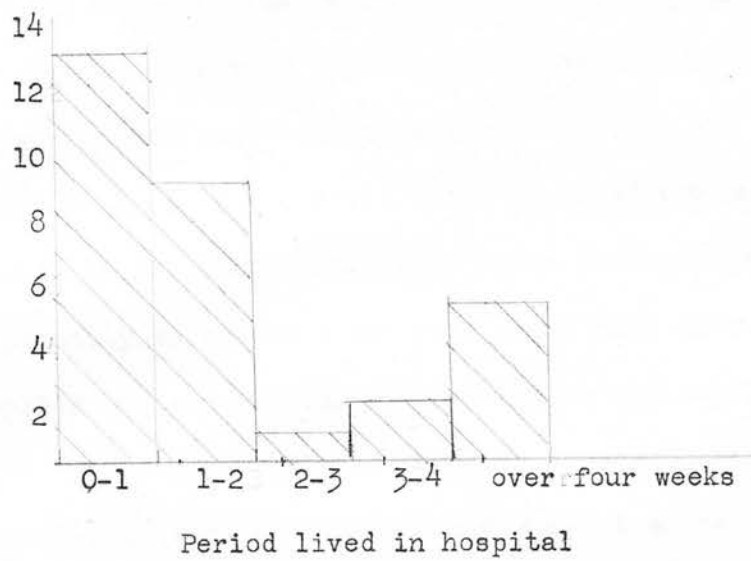


CHART 2



there have been few contributions to the subject. Gittens analysis of fourteen cases was published in 1933. All of these cases were studied carefully both clinically and haematologically and had autopsies performed. They form a noteworthy contribution. He remarks on the surprisingly few papers that have been written on leucosis, in children. As recently¹⁸ as 1940 Piney in his article which included two cases of myeloblastic leucosis in children states that acute leucosis is so protean a disease and possibly so common a one that every case should be recorded in order to enable proper clinical pictures to be put together.

The purpose of this paper is to present the findings of cases of leucosis observed in the Edinburgh Royal Hospital for Sick Children during the past twenty years. This hospital cared for practically all children requiring hospitalisation in the city of Edinburgh and district. The population of this area is approximately half to three quarters of a million people. Of the thirty cases included twenty had autopsies performed. The clinical records were in varying degree of completeness. Some cases died so rapidly that full investigations were not possible. The post mortem examinations were all performed by the pathology department and the majority by the same pathologist.

In addition to the above thirty cases there were seven more which were indexed as leucosis. Two of these records were missing. The other five cases, including two cases with post mortem, were inconclusive either due to the difficult clinical and pathological picture or due to insufficient clinical and haematological investigations.

Nomenclature.

Virchow in his original description used the term leukaemia, white blood. As the disease is not one wholly connected with the blood, but rather with the leucopoetic tissues throughout the body, leucosis is a more suitable term. The disease of leucosis may be a lymphadenosis or myelosis. Some writers divide these into aleucocythaemic, without definite increase in leucocytes but with qualitative changes of lymphadenosis or myelosis and aleukaemic where there is neither qualitative nor quantitative changes present. This division appears unnecessary as any given case may pass through all stages. Throughout this paper the term leucosis will be used.

(In cases, POST MORTUM
to read POST MORTEM.)

CASE 1

P.M. male, aged five years. Admitted 18/9/41 with symptoms of listlessness, drowsiness, pallor, anorexia, loss of weight and enlarged glands of neck. Symptoms commenced one month ago and worse recently. Sore throat and rash for several days.

EXAMINATION: Very ill; pallor; purpuric rash on limbs. Slightly thin. Enlarged glands of neck, axilla and groin. Liver two inches below costal margin. Spleen not palpable. Temperature 104°. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 2.0 M., Hb 45%; C.I. 1.1; W.B.C. 4,000. Neutrophile polymorphonuclears 4%, prelymphocytes 4%, indefinite cells 2% and lymphocytes 90%. Following day Hb 25% and W.B.C. 20,000 with lymphocytes 100%. Patient died day after admission.

POST MORTUM: Stomatitis and pharyngitis. Lungs oedematous with numerous small haemorrhages. Liver enlarged and cut surface has streaks and mottling suggestive of leukaemic infiltration. Spleen considerably enlarged. Kidneys slightly enlarged, no definite infiltration seen. Upper abdominal lymph glands enlarged. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow is entirely cellular. Small patches contain erythroblastic elements and groups of myelocytes but otherwise crowded with cells of lymphoid types. Liver; dense infiltration of portal tracts with hardly any involvement of the lobules. Spleen; sinuses crowded with leukaemic cells and atrophy of the pulp cells. Lymph gland; normal architecture obscured. All parts of gland crowded with leukaemic cells. Kidney; patches of leukaemic infiltration in the cortex. Lung; leukaemic infiltration present in distribution of the lymphatic plexus.

DIAGNOSIS: Lymphadenosis.

CASE 2

J.C., male, aged two years three months. Admitted 4/8/41 with history of not picking up since he had a boil on thigh six weeks before. Two weeks ago throat became sore and glands of neck enlarged. Increasing pallor. Rash for two days. Previous history, nothing of note. Family history, father age forty-five and mother age forty-one both alive and well. Patient second youngest of thirteen children. The sixth child died of lymphadenosis, see below.

EXAMINATION: Good development and nutrition. Marked pallor; petechial haemorrhages over whole body. Moderate enlargement of cervical glands, slight of groin. Mouth and throat ulcerated. Liver and spleen not enlarged. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.9 M., Hb 30%; C.I. 0.8; W.B.C. 8,000. Neutrophile polymorphonuclears 8.5%, eosinophil polymorphonuclears 0.5% typical large and small lymphocytes 68%, primitive lymphocytes and lymphoblasts 17.5% monocytes 2.5% and unidentified cells 3%. No nucleated red cells seen. Sternal puncture; great increase in lymphocytes and their precursors.

PROGRESS: Lived one week. Palpable shotty glands in axilla last few days of life. W.B.C. never above 10,000 and down to 4,000 on day before death and 250 on day of death.

POST MORTUM: Lungs and heart show petechial haemorrhages. Liver not enlarged. Spleen not enlarged but haemorrhagic area in substance. Glands of hilus and mesenteric group slightly enlarged and moderate enlargement of glands along great vessels to groin. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow of rib and femur intensely cellular and mostly lymphoid cells. A certain number of granular series and erythroblastic cells but much fewer than in normal marrow. Spleen; general architecture is well preserved. Malpighian bodies well defined. Some excess of lymphocytes in sinusoids of the pulp. No fibrosis. Liver; slight excess of cells in portal tracts but less than usual in leucosis. In addition to lymphocytes, eosinophils are conspicuous. No excess of cells in sinusoids. Mesenteric lymph gland and kidney appear normal.

DIAGNOSIS: Lymphadenosis with unusually slight visceral infiltration.

CASE 3

(Particulars of this case obtained from a letter from the Glasgow Royal Hospital for Sick Children).

T.C., male, aged one year eight months. Admitted 25/2/32 for pallor and epistaxis.

EXAMINATION: Small but well nourished. Pallor. Few petechial spots and some ecchymosis. Glands of neck, axilla and groin shotty but no larger than a pea. Liver one finger breadth below costal margin. Spleen not palpable.

BLOOD COUNT: R.B.C. 1.1 M., Hb 19%, C.I. 0.9; W.B.C. 19,000. Neutrophils polymorphonuclears 5.5%, small lymphocytes 75.5%, large lymphocytes 13.0%, transitional cells 5.5% and myelocytes 0.5%. Nine nucleated red cells seen in counting two hundred white cells.

Bleeding time prolonged, coagulation time 140 seconds, and no increased fragility. Wasserman Reaction negative.

PROGRESS: Given transfusion, iron, etc., but no genuine improvement although child lived for two months. On one occasion W.B.C. 28,200 but usually

in vicinity of 3,000 to 6,000. At no time could the spleen be palpated nor did the glands become very large. Four weeks after admission biopsy of axilla gland showed "the normal gland has been replaced by lymphocytes. The appearance are suggestive of lymphatic leukaemia or pseudoleukaemia". The pathologist on discussing this case with the clinician felt that this was most likely one of a leukaemic lymphadenosis. Permission for autopsy was refused.

DIAGNOSIS: Lymphadenosis.

CASE 4

C.P., female, aged two years. Admitted 2/7/41 with symptoms of increasing pallor for one month. Oedema of face for one week and feet for one day. Appetite good.

EXAMINATION: Very pale, oedema of face and to less degree of legs. Thin, Liver slightly enlarged, spleen palpable just below costal margin. No palpable glands of neck, axilla or groin. Other systems. No appreciable disease. Urine examination negative.

BLOOD COUNT: R.B.C. 0.74 M., Hb 17%; C.I. 1.1 W.B.C. 33,800. Neutrophile polymorphonuclears 9.5%, neutrophile myelocytes 0.5%, small lymphocytes 44%, large lymphocytes 35.5%, monocytes 1% and doubtful cells 9.5%. "Many of the cells classed as large lymphocytes were of primitive type, some definitely lymphoblasts; few normablasts".

PROGRESS: Several transfusions given and haemoglobin raised to 68% with a normal white count. Within one month child was running about the ward and so well that original diagnosis was doubted. Sent to convalescent home where condition deteriorated and W.B.C. 50,000 to 145,000, mainly small and large lymphocytes. Died two months after original admission to hospital.

POST MORTUM: Very advanced oral sepsis involving one inch of trachea and two inches of oesophagus. Enlargement of cervical and bronchotracheal glands in relation to this. Unresolved pneumonia left lung. Liver and spleen markedly enlarged. Abdominal glands enlarged. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Leukaemic infiltration of portal tracts but to less degree than usual. Spleen; Malpighian bodies small and each surrounded by a ring of congestion. Sinusoid walls are thick and cellular mainly due to infiltration of lymphocytes. Abdominal lymph gland; loss of normal architecture. Diffusely infiltrated with lymphocytes, many of a primitive type. Films of bone marrow and blood; the peroxidase reaction applied to these films failed to demonstrate any granules in the cells. In spite of post mortum changes the method would probably have been successful to some extent if the cells had been primitive granulocytes.

DIAGNOSIS: Lymphadenosis with unusually slight visceral infiltration.

CASE 5

J.S., male, aged five months. Admitted 11/6/41 with history of profuse sweating commencing two weeks before and followed a few days later by dark stools. Appetite poor and increasing pallor.

EXAMINATION: Good development and nutrition. Marked pallor. No glandular enlargement. Petechial on gums and palate. Throat healthy. Liver and spleen not enlarged. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.4 M., Hb 24%; C.I. 0.9; W.B.C. 11,000. Neutrophil polymorphonuclears 4%, metamyelocytes 3%, small lymphocytes 36% large lymphocytes 17%, primitive cells 39% and monocytes 1%. The lymphocytes are frequently of primitive type.

PROGRESS: Some improvement with first transfusion but then steady deterioration. Spleen never much enlarged and glandular enlargement late in appearing. Only terminally did W.B.C. rise above 10,000 when, three days before death, it was 21,000. Died four weeks after admission.

POST MORTUM:- Slight enlargement of cervical, inguinal, thoracic and abdominal lymph glands. Lungs show patch of consolidation. Heart pale, otherwise normal. Liver slightly enlarged and faint grey mottling present. Spleen slightly enlarged. Lymphoid tissue of ileum prominent. Several patches have small, firm, raised, whitish plaques suggestive of leukaemic deposits. One such plaque on ascending colon. Kidneys pale, enlarged and show infiltration. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow entirely cellular and mostly cells of lymphoid series. Slight erythroblastic activity. Lymph gland; leukaemic infiltration with normal architecture obscured but not entirely lost. Liver; leukaemic infiltration of varying degree but confined to portal tracts. Dense in few places only. Spleen; slight leukaemic infiltration. Kidneys; very severe leukaemic infiltration. Intestine; nodules of leukaemic deposits chiefly in submucosa but also in muscular and subserous layers. Mucosa necrotic over these deposits and inflammatory cells mingle with leukaemic cells. Lung consolidation due chiefly to a cellular exudate of fibrin and oedema. Many bacteria but a complete failure of usual reaction to bacteria.

DIAGNOSIS: Lymphadenosis.

CASE 6

J. MacK., female, aged seven years. Admitted 14/9/40 with symptoms of swelling of neck, listlessness, increasing pallor, anorexia, and loss of weight of five weeks duration. Sore throat for one week. Earlier in illness seen at surgical out-patient department and diagnosis of tuberculous adenitis was made.

EXAMINATION: Pallor with yellowish tinge. No rash. Thin.

Palpable glands in neck, axilla and groin from size of pea to size of walnut. Mouth and throat healthy but tonsils enlarged. Liver four fingers breadth below costal margin. Spleen three fingers breadth below costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 3.3 M., Hb 66%, C.I. 1.0, W.B.C. 31,600.

Lymphocytes 99% and polymorphonuclears 1%. Three days later Hb 40% and W.B.C. 9,000 with lymphocytes 100%. Sternal puncture: Cellular marrow, nearly all of lymphoid series.

Patient died six days after admission.

POST MORTUM: Enlarged mediastinal and abdominal lymph glands as well as superficial groups. Epiglottis and aryepiglottic folds immensely swollen and ulcerated. Lungs; small healed tuberculous focus. Oedematous lungs. Liver much enlarged with pearly grey streaks suggestive of leukaemic infiltration. Spleen moderately enlarged. Kidneys of average size with haemorrhagic masses of infiltration. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow entirely cellular with slight erythroblastic activity. Nearly all the cells are of lymphoid series. Lymph gland crowded with leukaemic cells. Liver; large amount of portal tract infiltration. Cells practically all small lymphocytes. Slight excess of these cells in sinusoids. Spleen; moderate degree of leukaemic infiltration. Kidneys; leukaemic infiltration of varying degree in different areas.

DIAGNOSIS: Lymphadenosis.

CASE 7

C.B; female, aged eleven and a half years. Admitted 20/6/40 with history of anorexia and vomiting for one month, loss of weight and listlessness for two weeks. Previously healthy and always large and heavy for her age.

EXAMINATION: Large, healthy looking girl. Mouth healthy.

Impairment of movement and percussion note of left chest. Vesicular breath sounds but diminished intensity and vocal resonance of left side. Liver and spleen not enlarged. Lower poles of both enlarged kidneys palpable despite good nutrition and muscle tone. These masses considered as abdominal glands but subsequently confirmed as kidneys. No palpable cervical, axilla or inguinal glands. Other systems, no appreciable disease. X-ray; "Extreme fluid exudate left side" Diagnostic aspiration of 10 cc. pleural fluid showed straw coloured fluid containing lymphocytes and no organisms. Urine normal.

BLOOD COUNT: Hb 95%, W.B.C. 8,100. Neutrophil polymorphonuclears 80%, basophil polymorphonuclears 1%, lymphocytes 13% and monocytes 6%. R.B.C. normal in size and shape. Platelets moderately plentiful.

PROGRESS: Provisional diagnosis of tuberculosis was made but tuberculin reaction negative. After three weeks clinical condition stationary and diagnosis doubtful. Clinical and radiological findings of chest did not agree and decided to aspirate as much fluid as possible before repeating X-ray. No fluid obtained. X-ray, no fluid; mediastinal tumour suggests lymphosarcoma. Previous inaccurate report due to tumour plus small amount of free fluid which had now resolved. Patient continued to have vomiting and bilateral papilloedema found. Lumbar puncture; fluid normal pressure and biochemical and cytological examinations normal.

In the next four weeks condition stationary. Haemoglobin continued in region of ninety per cent with normal leucocyte count. However, film showed anisocytosis and a few normablasts and this was followed by some lymphoblasts. The blood picture changed from a predominant polymorphonuclear one on admission to a lymphocytic one with W.B.C. 15,800. Neutrophil polymorphonuclears 14%, eosinophil polymorphonuclears 1%, basophil polymorphonuclears 1%, monocytes 5%, small lymphocytes 11%, medium and large lymphocytes 65%

and lymphoblasts 3%. Sternal puncture showed an actively cellular marrow with 97% of lymphocytic series, mostly lymphoblasts and 3% of the granular series, chiefly metamyelocytes. A few days later spontaneous bruising appeared and continued for remaining five weeks of life. Palpable gland in axilla noted and ten days before death cervical and inguinal glands also palpable. Liver enlarged three fingers breadth below costal margin but spleen never palpable. Condition deteriorated, haemoglobin falling to fifty five per cent two days before death. W.B.C. never above 18,000 and lymphoblasts never numerous. In latter weeks complained of sternal pain. Had several treatments of X-ray radiations but caused systemic upset. Died three months after admission.

POST MORTUM: Brain; subacute purulent meningitis the origin of which was not discovered. Thorax; mass in anterior mediastinum overlying the heart. Thoracic glands moderately enlarged. Liver considerably enlarged and greyish streaks suggestive of leukaemic infiltration. Spleen a little enlarged. Kidneys enormously enlarged with severe infiltration. Enlarged lymph glands along the aorta. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow; slight erythroblastic activity. Cellular and almost all lymphoblasts and lymphocytes. Lymph gland; dense leukaemic infiltration. Liver; heavy infiltration along portal tracts and a small amount through lobules. Liver cells healthy. Spleen; very little leukaemic infiltration* Suprarenal; considerable amount of leukaemic infiltration especially in medulla. Heart; slight leukaemic infiltration under epicardium but not in myocardium. Mass in anterior mediastinum largely fibrous with a certain amount of leukaemic infiltration and no thymus tissue recognisable.* Kidneys; heavy leukaemic infiltration.

DIAGNOSIS: Lymphadenosis with meningitis.

BLOOD COUNT: R.B.C. 1.7 M., Hb 28%; C.I. 0.8, W.B.C. 164,200.

Film shows almost all cells large with a relatively large, round nucleus and in many cases prominent nucleoli. Cytoplasm basophilic, non-granular and negative to peroxidase stain. A few small lymphocytes, occasional polymorphonuclears and no myelocytes.

PROGRESS: Child lived six days. W.B.C. decreased daily until day before death it was 24,600 with primitive cells much fewer and most of cells normal large and small lymphocytes. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

CASE 25

T.B., male, aged four years one month. Admitted 12/11/30 with history of not being well since tonsillectomy five months before. Glands of neck enlarged two weeks ago and for one week abdomen distended and purpuric spots present.

EXAMINATION: Face pale and puffy. No oedema of limbs. Purpuric rash. Cervical, axilla and inguinal glands enlarged. Mouth and throat healthy. Liver one inch below umbilicus. Spleen one hand breadth below costal margin. Urine positive for albumin but otherwise normal. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 5.4 M., Hb 60%; C.I. 0.6; W.B.C. 28,400. Small lymphocytes 96%, myelocytes and large lymphocytes 2% and neutrophil polymorphonuclears 2%.

PROGRESS: Lived nine days. Had bleeding from gums. Melaena. Never any haematuria. ~~melæna~~. Haemoglobin fell rapidly. W.B.C. up to 56,000 with 97.5% lymphocytes. Rapid diminution of size of liver and spleen before death. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

CASE 8

M.A., female, aged four years three months. Admitted 27/2/39 with history of pallor, listlessness, anorexia and loss of weight for six months. Passed tarry stools on day of admission.

EXAMINATION: Fair nutrition. Marked pallor. Few purpuric spots. Few cervical glands palpable. Throat healthy. Liver and spleen not enlarged. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.1 M., Hb 19%, C.I. 0.9, W.B.C. 5,600. Patient died on day of admission.

POST MORTUM: Patch of pneumonic consolidation. Subpleural, subepicardial and endocardial patchiae. Liver slightly enlarged. Spleen definitely enlarged but not greatly so. No visible blood in alimentary tract but some submucous haemorrhages in stomach. Kidneys; haemorrhages into substance of kidneys. Thoracic lymph glands slightly enlarged but no enlargement of abdominal glands. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow cellular. Main type is a primitive non granular cell probably a myeloblast. Very little erythroblastic activity. No mature granulocytes. Lymph gland; normal appearance with no leukaemic infiltration. Spleen; considerable infiltration of pulp with leukaemic cells but Malpighian bodies still quite distinct. Liver; leukaemic infiltration which is dense in portal tracts but considerable numbers throughout lobules. Cells fairly large with vesicular sometimes indented nucleus and nongranular cytoplasm. Kidneys; both show areas of leukaemic infiltration and superadded haemorrhage.

Pathologists summary; cell type and distribution of infiltrations indicate myelosis. Absence of characteristic changes in lymphoid structures is against lymphadenosis.

DIAGNOSIS: Leucosis, probably myelosis.

CASE 9

J.C., male, aged one year two months. Admitted 17/11/36 with history of being "off colour" for one month. Purpuric spots appeared one week ago and followed by black, swollen gums and vomiting. Child is a twin.

EXAMINATION: Thin. Marked pallor with purpuric spots. Slight enlargement of cervical, axilla and inguinal glands. Gums discoloured and bleeding. Tonsils enlarged but tonsils and pharynx healthy. Blood in stools. Liver and spleen not enlarged. Systolic murmurs in mitral and pulmonary areas. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.1 M.; Hb 15%; C.I. 0.7; W.B.C. 5,000
Differential count on 317 cells: neutrophil polymorphonuclears 1.9%
Eosinophil polymorphonuclears 0.6%, basophil polymorphonuclears 0.3%, monocytes 1.9%, lymphocytes 74.1% and lymphoblasts 21.1%. "Film of lymphadenosis as lymphocytic elements preponder and there is 21.1% of lymphoblasts as recognised by size and nucleoli. Polychromasia present and one normoblast seen".

PROGRESS: Child lived for nine days after admission. Three days before death W.B.C. 20,000 with 100% lymphoblasts.

POST MORTUM: Permission limited to removing a portion of marrow from femur but through this incision it was found possible to obtain a small fragment of liver. Liver and spleen palpated but not appreciably enlarged.

MICROSCOPIC EXAMINATION: Bone marrow cellular but not obviously abnormal for age. No special preponderance of any particular type of cell. Liver; fatty degeneration but no cellular infiltration; suggests profound anaemia but does not show any evidence of leukaemic infiltration.

BLOOD COUNT: R.B.C. 1.7 M., Hb 28%; C.I. 0.8, W.B.C. 164,200.

Film shows almost all cells large with a relatively large, round nucleus and in many cases prominent nucleoli. Cytoplasm basophilic, non-granular and negative to peroxidase stain. A few small lymphocytes, occasional polymorphonuclears and no myelocytes.

PROGRESS: Child lived six days. W.B.C. decreased daily until day before death it was 24,600 with primitive cells much fewer and most of cells normal large and small lymphocytes. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

CASE 25

T.B., male, aged four years one month. Admitted 12/11/30 with history of not being well since tonsillectomy five months before. Glands of neck enlarged two weeks ago and for one week abdomen distended and purpuric spots present.

EXAMINATION: Face pale and puffy. No oedema of limbs. Purpuric rash. Cervical, axilla and inguinal glands enlarged. Mouth and throat healthy. Liver one inch below umbilicus. Spleen one hand breadth below costal margin. Urine positive for albumin but otherwise normal. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 5.4 M., Hb 60%; C.I. 0.6; W.B.C. 28,400.

Small lymphocytes 96%, myelocytes and large lymphocytes 2% and neutrophil polymorphonuclears 2%.

PROGRESS: Lived nine days. Had bleeding from gums. Melaena. Never any haematuria. Haemoglobin fell rapidly. W.B.C. up to 56,000 with 97.5% lymphocytes. Rapid diminution of size of liver and spleen before death. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

DIAGNOSIS: Lymphadenosis. In view of the clinical picture and haematological findings which were performed by an experienced haematologist the diagnosis of a leucosis is definite. The fact that the portion of marrow examined was normal and that there was no hepatic infiltration as usually found does not alter the original diagnosis.

CASE 10

W.Q., male, aged two and a half years. Admitted 2/3/36 with history of flitting pains in legs and arms for three weeks. Knees occasionally swollen. Spots on neck for three days and testicular swelling for one day. Increasing pallor and weakness. No response to salycilate therapy.

EXAMINATION: Thin, Pale colour. Petechiae. Few palpable glands in inguinal region but not elsewhere. Liver two fingers breadth below costal margin. Spleen three fingers breadth below costal margin. Pulmonary systolic murmur. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 4.7 M., Hb 66%, C.I. 0.7, W.B.C. 22,500. Neutrophile polymorphonuclears 12%, eosinophile polymorphonuclears 1%, lymphocytes 12% basophile polymorphonuclears 1.5%, neutrophile myelocytes 1.5% monocytes 3.5%, and primitive cells 68.5%. The primitive cells are relatively large with basophil non-granular cytoplasm and a nucleus resembling that of a myeloblast or lymphoblast. A few normoblasts seen.

PROGRESS: Steady deterioration and profuse haemorrhages from mucous membranes and into skin. Died ten days after admission.

POST MORTUM: Enlargement of glands at root of neck and gross enlargement of paraortic lymph glands. Pharynx healthy. Lungs show few haemorrhages. Heart has extremely numerous haemorrhages not only subepicardial but into myocardium. Liver considerably enlarged and shows

CASE 26

W.H., male, aged eight months. Admitted 14/12/29 with history of abdomen enlarging for four months. Not thriving for past month. Enlarged glands of groin for three weeks.

EXAMINATION: Well grown but thin. Pallor. Enlarged axilla and inguinal glands. Mouth and throat healthy. Liver three fingers breadth below costal margin. Spleen enlarged to umbilicus. Other systems no appreciable disease.

BLOOD COUNT: R.B.C. 3.3 M., W.B.C. 191,200. Film shows hypochromic red cells. Leucocytes are mostly myelocytes.

PROGRESS: In hospital two weeks and had three treatments with X-ray with no change in size of spleen. Deteriorated rapidly and taken home to die.

DIAGNOSIS: Myelosis.

CASE 27

J.O., male, age five years four months. Admitted 25/3/29 with history of jaundice six weeks ago which cleared up. Four weeks ago pains in legs followed by bruising and right sided abdominal pain. Increasing weakness and pallor.

EXAMINATION: Moderate nutrition. Marked pallor. Purpuric rash. Cervical, axilla and inguinal glands enlarged. Mouth healthy. Liver enlarged to umbilicus and spleen half way to umbilicus. Retinal haemorrhages. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.8 M., Hb 28%, C.I. 0.8; W.B.C. 112,000. Large lymphocytes 99%, small lymphocytes 0.7% and neutrophil polymorphonuclears 0.3%. Occasional nucleated red cell.

PROGRESS: Steady deteriorated and died on fourth day. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

CASE 28

T.M., male, age two years eight months. Admitted 5/10/27 with history of lassitude and pallor for three months. Two months ago blood in stool but no diarrhoea. Urine dark. Bruises easily and bleeding from gums for two weeks.

EXAMINATION: Marked pallor. Purpuric rash. Diagastric glands enlarged. Liver one inch below costal margin. Spleen palpable at costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 2.2 M., Hb 40%, C.I. 0.9; W.B.C. 44,000. Small lymphocytes 88%, large lymphocytes 10% and neutrophil polymorphonuclears 2%.

PROGRESS: Deteriorated rapidly and died one week after admission. Increasing purpura in interval. W.B.C. 22,000 to 44,000 and almost all lymphocytes. Post mortum not obtained.

DIAGNOSIS: Lymphadenosis.

CASE 29

J.H., female, aged two years five months. Admitted 5/2/23 with history of listlessness for three months and spots on legs for two months. Condition steadily becoming worse. Epistaxis two days ago.

EXAMINATION: Good development and nutrition. Marked pallor and purpuric rash on legs. No enlargement of lymph glands. Gums healthy. Liver not enlarged. Spleen palpable. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 0.9 M., Hb 12%; C.I. 0.7; W.B.C. 152,000. Film report "Probably a myeloblastic leukaemia". Patient died soon after admission and post mortum not obtained.

DIAGNOSIS: Leucosis, probably myelosis.

fine white streaks suggestive of leukaemic infiltration. Spleen greatly enlarged. Kidneys greatly enlarged and very extensive infiltration with superadded haemorrhage. Numerous haemorrhages in mesentery. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow is hyperplastic. Chief cell is primitive, non-granular cell. A few myelocytes present. Very little erythroblastic activity. Lymph gland; loss of normal architecture and gross infiltration of leukaemic cells. Liver; gross leukaemic infiltration in portal tracts but so dense that it encroaches on lobules. Leucocytes increased in sinusoids but no real infiltration. Some of the hepatic veins show infiltration in their adventitial spaces. Spleen; diffuse infiltration of the characteristic cell. Kidney; severe infiltration of both kidneys. Lungs; a little infiltration of perivascular stroma. No pneumonia.

DIAGNOSIS: Leucosis, probably lymphadenosis

CASE 11

M.H., female, aged five years three months. Admitted 26/10/33 with history of being perfectly well until ten days before when spontaneous bruising occurred. Bruises increasing and, in last day, epistaxis, haematemesis and melaena, occurred.

EXAMINATION: Well nourished. Marked pallor. Purpuric spots over body. Enlarged glands in neck, axilla and inguinal regions. Incomplete examination as condition critical. Child died before transfusion could be given.

POST MORTUM: No stomatitis. Lungs oedematous and blood stained pleural effusion. Heart pale and petechiae present. Liver average size with white streaks suggestive of leukaemic infiltration. Spleen much enlarged.

CASE 30

G.V., male, aged seven years eight months. Admitted 3/2/22 with history of swollen feet six weeks ago followed by swollen hands and headache. Bilateral discharge from ears. During last week had abdominal pain.

EXAMINATION: Good nutrition. Pallor. No rheumatic nodules. Slight swelling of right wrist, other joints unaffected. Tonsils and adenoids enlarged and discharging left ear. Urine normal.

PROGRESS: Five days after admission adenoids removed. Four days later noted cervical and inguinal glands enlarged and liver and spleen enlarged.

BLOOD COUNT: R.B.C. 3.6 M., Hb 70%; C.I. 1.0; W.B.C. 114,200. Small lymphocytes 49%; large lymphocytes 48.5% and neutrophil polymorphonuclears 2.5%. Condition steadily deteriorated with glands enlarging and the appearance of purpuric spots. White cell count on several occasions in vicinity of 150,000. One month after admission child taken home to die.

DIAGNOSIS: Lymphadenosis.

Kidneys pale and questionable infiltration. Numerous petechial haemorrhages of peritoneum. Blood in stomach and intestine but no gross ulceration only numerous submucous haemorrhages. Thoracic and abdominal glands enlarged as well as superficial groups. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow cellular. Erythroblastic elements scarce. Numerous undifferentiated cells with non-granular cytoplasm and round or indented nucleus. Many small lymphocytes, Myelocytes present, eosinophil type being conspicuous. Lymph gland; normal architecture obscured by dense infiltration of above cells. Spleen; dense infiltration of cells of size and appearance of large and small lymphocytes. Liver; portal tract infiltration. Sinusoids also crowded with leucocytes but this appears to be due to large number in circulation rather than to true infiltration. Kidney; all leukaemic cells appear to be in the blood vessels and no true interstitial infiltration seen. Lungs; oedematous. No leukaemic infiltration.

POST MORTUM BLOOD FILM: 11m; Enormous increase in leucocytes which seem nearly as numerous as the red cells. Practically all are mononuclear cells with blue staining, non-granular cytoplasm. The majority are the size of large lymphocytes but with larger nucleus and less cytoplasm while some of these primitive cells are little larger than small lymphocytes. No nucleated red cells seen. Differential count; primitive cells 60%, small lymphocytes 39% and granular cells 1%.

DIAGNOSIS: Lymphadenosis of exceptionally fulminating character.

DISCUSSION AND COMMENT.

The study of this series of cases impresses one with the fact that leucosis is not a very rare disease. When one considers the difficulty in accurate clinical diagnosis and the rapidity of death in some cases it appears probable that some cases of leucosis died at home and a diagnosis of anaemia, scurvy or purpura was made.

Nearly one half of this series was dead inside of a week after admission to hospital (See Chart 1.) A considerable number died one or two days after coming to hospital. Only five cases lived over one month after admission. The onset of symptoms was insidious in practically all of the cases and on an average they were of three to four weeks duration. Some cases had symptoms for as long as three months while a few had them for as short a time as ten days.

This disease is one of early childhood. The youngest of this series was eight months and the oldest eleven and a half years. The age limit of admission to this hospital is 12 years. Of the thirty cases sixteen were under the age of three years. The age of two to three years was that of greatest incidence, with ten cases. (See Chart 2.)

There were nineteen males and eleven females which is in keeping with the increased prevalence in males which is recorded in the literature.

The symptomatology has many points in common with numerous diseases, both blood dyscrasias and general diseases. Atypical cases are common but some of the most frequent findings are anaemia with pallor, haemorrhages into the skin and from the mucous membranes, anorexia, listlessness, enlarged glands, spleen and liver and an irregular fever. The symptoms and signs may be aggravated by the degree of anaemia and by the frequency of superadded

CASE 12

T.G., male, aged two years four months. Admitted 11/11/32 with history of progressive pallor for one month, poor appetite and listlessness for one week and vomiting for the last three days. No bleeding from mucous membranes.

EXAMINATION: Thin. Marked pallor with few purpuric spots. Moderate enlargement of cervical, axilla and inguinal glands. Mouth healthy. Basal systolic murmur. Liver and spleen not enlarged. Other systems, no appreciable disease. Wassermann reaction and tuberculin reaction negative.

BLOOD COUNT: R.B.C. 0.8 M., Hb 13%; C.I. 0.8; W.B.C. 4,100 Small lymphocytes 33%, large primitive cells 60%, neutrophil polymorphonuclears 4%, eosinophil polymorphonuclears 1% and eosinophil myelocytes 2%. The primitive cells are large with non-granular cytoplasm and pale nucleus. In a few cells nucleolus present. No granules by the peroxidase stain. No nucleated red cells.

PROGRESS: Patient received a number of transfusions and multiple drug therapy and lived for three and a half months. There was no change in size of glands. In latter weeks spleen palpable and one week before death it was two fingers breadth below costal margin. White cell count tended to rise and on day of death it was maximum at 44,200.

POST MORTUM: Thin. Extreme pallor. No petechia. Mouth and pharynx healthy. Heart shows petechial haemorrhages and lungs oedematous. Slight enlargement of trachea-bronchial and mesenteric lymph glands. Liver pale and slightly enlarged. Spleen slightly enlarged. Kidneys grossly enlarged and numerous small haemorrhages present. Stomach has nodular elevations of the wall. Other organs, no appreciable disease.

secondary infections. Stomatitis is not uncommon. The nutrition is usually good, especially in the more acute cases. Some workers, notably Forkner,⁹ have attempted to differentiate varying clinical groups of acute leucosis by haematological methods. A study of the present series leads one to believe that there is no clinicopathologic picture which is characteristic of the cell type of the leucocytes. This is in keeping with the findings of most observers.

ANAEMIA

Anaemia is an almost constant feature and in most cases it is of a severe degree. The diagnosis of acute leucosis with a haemoglobin of 85%, as in case 7, is most unusual. Although pernicious anaemia is the classic example of a disease where a severe anaemia is present before medical advice is sought leucosis can share in this feature. Haemoglobin readings of 20% to 50% were usual on admission. Nucleated red cells were found frequently. In sixteen cases, where specific reference was made, eight had nucleated red cells and an equal number had none.

Gittens¹⁰ states that abnormality of the erythron is unusual in leucosis and seldom seen in lymphadenosis but this series does not bear this out.

LEUCOCYTES.

The leucocyte findings present many interesting features. There were twenty two cases of lymphadenosis and of these there were eight cases with a marked leucocytosis, that is, above 40,000 cells per cu. mm. There were eight cases which were never above 20,000 cells. The most common feature was a moderate leucocytosis of 15,000 - 30,000. Some of the cases in the first group, of marked leucocytosis, did have lower counts during some stage of their illness. Of all the lymphadenosis cases nearly half had a normal count or leucopenia during the whole or part of the time under observation.

MICROSCOPIC EXAMINATION: Bone marrow cellular. Erythroblastic elements scanty. Main cell is a moderately large cell with non-granular cytoplasm and a large indefinitely stained nucleus. Occasional myelocyte. Spleen; Malpighian bodies difficult to recognise and excess lymphocytes in pulp. Liver; portal tract leukaemic infiltration. Kidneys; extremely dense infiltration. Lung; oedematous. Infiltration in perivascular tissues and to lesser extent around large bronchi. Stomach; dense leukaemic infiltration in mucous and submucous layers.

DIAGNOSIS: Lymphadenosis.

CASE 13

E.R., female, aged one year six months. Admitted 20/7/32 with a history of pallor and listlessness for two months. Appetite poor. No bleeding from any mucous membrane.

EXAMINATION: Good nutrition. Extreme pallor. Several palpable glands in neck, axilla and inguinal region. Liver not enlarged. Spleen half way to umbilicus. Other systems, no appreciable disease. Wassermann reaction and tuberculin reaction, both negative.

BLOOD COUNT: R.B.C. 2.5 M., Hb 30%; C.I. 0.6; W.B.C. 7,000. Lymphocytes 90% and neutrophil polymorphonuclears 10%. A number of the lymphocytes are of a primitive type. No nucleated red cells.

PROGRESS: Patient lived for six months after admission. Transfusions gave a temporary improvement. Numerous drugs given with no obvious improvement. Spleen increased in size and later decreased spontaneously. Following radium therapy it decreased further and on 6/12/32 splenectomy performed. Following operation a clinical improvement was noted but a deterioration then set in and patient died seven weeks after splenectomy.

In the myelosis cases a marked leucocytosis was common and it was of a more severe degree. In seven of the eight cases the leucocyte count varied between 57,200 and 360,000. Allowing for the prevalence of leucocytosis in myelosis cases it will be seen that in the whole series of leucosis only 50% of the cases had a marked leucocytosis during the whole or part of the time under observation. This finding is in keeping with the more recent series presented in the literature and contrasts with Ramsay's²⁰ cases where 85% had marked leucocytosis. No doubt this is accounted for by the fact that in the period covered by Ramsay's series, cases with high leucocyte counts tended to be recorded in the literature and a larger number of cases of leucosis with normal or lower counts were not diagnosed. The white count may have marked variations at different times. Cooke⁵ had a case with a reduction from 200,000 to 3,000 in three days and another from 107,000 to 11,500 in 4 days. Kracke¹⁶ states that in one of his cases with a count of 75,000 on admission it had decreased to 1,000 in four days and one week later it was 50,000. A fortnight later, on the day before death, the count was only 600. Kauffman¹⁴ records a case where the count went from 900 to 375,000 but does not state the time interval. In the present series there were several cases with a considerable range. Case 4 had a count of 8,600 on one occasion and some time later it was 145,000 only to fall to 21,000 in four days. The last count was on the day before death. Case 24 with a count of 164,200 steadily decreased for five days when the count was 24,600. Death occurred the following day. Case 6 had a count of 31,600 and 3 days later it was 9,000; death occurred 2 days later. Case 2 decreased from 6,000 to 250 on day of death, which was an interval

During period of observation there was little change in the size of the glands and there was no leucocytosis until the last few weeks of life when W.B.C. was in vicinity of 30,000.

POST MORTUM: Nutrition moderately good but pallor marked. Liver large and pale. Kidneys both much enlarged and numerous petechial ~~and~~ haemorrhages. Other organs; apart from effects of anaemia, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow is cellular. Majority are primitive cells of lymphocytic series. Relative absence of erythroblastic elements. Lymph gland densely packed with cells of lymphatic series. Liver; cuff of lymphocytes about portal tract and extending to one quarter the width of lobule. Very few cells infiltrating between the liver cells. Kidneys; massive leukaemic infiltration chiefly in the cortex and associated with haemorrhage. Spleen (from operation), increase in fibrous tissue. Excess of mononuclear cells in the pulp and relatively few red cells. There is a complete absence of cells of polymorphonuclear type.

DIAGNOSIS: Lymphadenosis.

CASE 14

M. D., female, age three and a half years. Admitted 25/5/32 with a history of being listless since whooping cough three months before. Abdomen enlarging for three weeks. Rash on body and limbs for four days but no bleeding from mucous membranes.

EXMINATION: Thin. Pallor with purpuric rash. No enlargement of cervical, axilla or inguinal glands. Abdomen distended. Spleen enlarged nearly to umbilicus. Liver three quarters of an inch below costal margin. No ascites. Other systems, no appreciable disease.

of three days. No doubt other marked fluctuations would have been found if more frequent counts had been performed. Associated with the variations in cell count is a changing differential count. In case 24, mentioned above, the first films showed nearly all lymphoblasts while five days later the more normal count was accompanied by a more normal film with a much less number of primitive cells and mostly large and small lymphocytes. In that short period a tremendous number of primitive cells were eliminated from the circulation. The more frequent finding in the film is a tendency for showers of primitive cells to appear terminally so that nearly all the cells then are primitive.

In those cases where platelet count was performed they were always reduced in number. This absence is responsible for the prolonged bleeding time and resulting haemorrhagic disorders. The platelet count may be of help in the differential diagnosis of atypical cases. In agranulocytosis with sepsis the picture may be difficult to distinguish from an aleukaemic leucosis and a normal platelet count in the former may be of great assistance. The platelets are also normal in infectious mononucleosis. However, in aplastic anaemia the platelets may be reduced but a sternal puncture will usually settle the diagnosis.

No case of this series was considered a monocytic leucosis. Court⁶ describes two new cases in childhood and draws attention to "atypical cells" which if they occur in large numbers may confuse the diagnosis. He suggests that this type of leucosis is probably more common than generally recognised at present. Kracke¹⁶ in discussing the question of monocytic leucosis states that recorded cases of such fall into two groups; one characterized by the presence in the peripheral blood of typical adult monocytes arising from

BLOOD COUNT: R.B.C. 3.7 M., Hb 62%; C.I. 0.8; W.B.C. 57,200.

Myeloblasts 36%, myelocytes 15%, neutrophil polymorphonuclears 32%, eosinophil polymorphonuclears 2%, basophil polymorphonuclears 1% and small and large lymphocytes 14%. Many nucleated red cells.

PROGRESS: Condition steadily deteriorated and died two weeks after admission. Two days before death W.B.C. 107,000 with 65% myeloblasts.

POST MORTUM: Emaciated. Purpuric spots. Liver slightly enlarged and shows grey mottling suggestive of leukaemic infiltration. Spleen greatly enlarged. Slight to moderate enlargement of glands of thorax and abdomen. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow is leucoblastic with myeloblasts and myelocytes predominating. Phagocytosis of red cells and white cells by large endothelial cells is a feature. Lymph gland; diffuse infiltration by the leukaemic cells. As in the marrow phagocytes are prominent. Spleen; infiltration by myelocytes and myeloblasts. Liver; well marked leukaemic infiltration through lobules and of portal tracts. Kidney; very slight leukaemic infiltration. Colon (ileo-caecal valve); lymphoid tissue of wall infiltrated with leukaemic cells. Phagocytes again conspicuous.

DIAGNOSIS: Myelosis.

CASE 15

A.H., male, aged nine years four months. Admitted 2/11/31 with history of cough, pain in chest and abdomen, vomiting and fever for past week.

EXAMINATION: Well developed. Pallor. Many enlarged glands in neck and one in inguinal region. Throat healthy. Physical signs of right sided pneumonia. Abdomen tender. Liver and spleen enlarged. Other systems no appreciable disease.

the reticulo-endothelium, and another type characterized by the presence of atypical myeloblasts that are incorrectly designated as monocytes or monoblasts.

LYMPH GLANDS

In the superficial lymph glands slight to moderate enlargement was the rule although several cases, lymphadenosis and myelosis, had no palpable enlargement. The enlargement of abdominal and thoracic glands was general and of a similar degree to the superficial group. The degree of thoracic or abdominal enlargement was no more marked in those cases where there was parenchymal infiltration in these cavities. The enlargement of the mediastinal glands or infiltration of thymus or other mediastinal tissue may give rise to mediastinal tumour which may be recognised by X-ray. Case 7 is an example. Cooke⁴ states that leucosis is the commonest cause of mediastinal tumour in childhood. She records that of thirteen such cases nine were due to leucosis.

The fact that in leucosis lymph gland enlargement is usually general and of moderate degree is of assistance in the clinical differentiation from lymphadenoma. In the latter, it usually affects one group of glands first and then spreads to other groups in an irregular manner and the degree of enlargement is greater.

SPLEEN

Splenic enlargement is usual. Of the cases with autopsy only one, a lymphadenosis, had no splenic enlargement. Several had slight enlargement but most had moderate or gross enlargement. In Cooke's⁵ series of fifty leucosis, all cases had splenic enlargement.

BLOOD COUNT: R.B.C. 3.2 M., Hb 70%, C.I. 1.1, W.B.C. 216,000.

Small and medium lymphocytes 11%, primitive cells 88%, neutrophil polymorphonuclears, 1.6%, neutrophil myelocytes 0.2% and eosinophil myelocytes 0.2%. The primitive cells are large with pale nucleus. Cytoplasm basophilic, non-granular in Leishman stain but granules with Oxydase stain. No nucleated red cells seen.

PROGRESS: Patient admitted to hospital as pneumonia. Condition improved but abdominal pain persisted and after the first week occipital and inguinal glands became enlarged and child rapidly deteriorated and died eleven days after admission.

POST MORTUM: Fairly well nourished. Marked pallor. Cervical, axilla, inguinal and mediastinal glands enlarged. Coeliac and upper abdominal group slightly enlarged, others hardly enlarged but of unusually shotty character, Bronchitis, bronchopneumonia and subpleural petechial. Heart flabby with subepicardial haemorrhages. Liver enlarged, pale and white spots through it. Spleen; much enlarged. Kidneys pale but no infiltration seen. Many petechial haemorrhages in peritoneum. Other organs, no appreciable disease.

MICROSCOPIOIC EXAMINATION: Bone marrow wholly cellular and almost all leucoblastic. Very few erythroblastic elements. Chief cell is a large one with non-granular cytoplasm and round nucleus. Some neutrophil and eosinophil myelocytes, hardly any polymorphnuclears and a few small lymphocytes. Lymph gland; normal structure obscured by infiltration. Spleen; leukaemic cell infiltration. Liver; leukaemic cell infiltration which is of diffuse character of myelosis. Kidney and heart show leukaemic infiltration and also the lung in non-pneumonic areas. Pancreas shows no infiltration.

DIAGNOSIS: Leucosis, probably myelosis.

LIVER

In three cases the liver was not considered enlarged at autopsy. Slight to moderate hepatomegaly was usual. In all but one case infiltration was reported on microscopic examination. In the lymphadenosis it was of portal tract distribution but in cases of severe infiltration it extended toward the centre of the lobules. Infiltration in myelosis was of sinusoid distribution. In cases of liver infiltration it was often possible to see it on examining the cut surface where there was a mottled and streaked appearance.

There are a number of references in the literature to rapid diminutions in size of spleen, and occasionally liver, shortly before death. Case 18 and Case 25 showed this feature.

ALIMENTARY TRACT

Stomatitis of severe degree was noted in five cases. In several the ulceration spread downwards to pharynx, larynx and oesophagus. All these cases were lymphadenosis and generally the granulocytes were leukopenic but, on the other hand, other cases with equally low granulocyte counts did not have ulcerative oral lesions. This is in keeping with the findings of Pierce¹⁷. In addition to the above there were cases with varying severity of haemorrhage from the mucous membranes of the oral cavity. Some of these latter lesions had infection superadded. In Cooke's⁵ review of fifty cases she noted ulcerative stomatitis in four cases.

In three cases, that is, fifteen percent of those having post mortem, naked eye infiltration of intestine was found. Case 12 had a nodular elevation of stomach wall which, on microscopic examination, showed dense infiltration of mucous and submucous layers. Case 5 had infiltration of all layers in ileo-caecal and ascending colon regions. The third one, case 14, also had ileo-caecal wall infiltration. This last case was a myelosis, the others being lymphadenosis.

CASE 16

R.M., male, aged four years ten months. Admitted 14/6/31 from a surgical ward with a history of taking ill two months previous with fever, listlessness and pain in left knee. One week after onset of symptoms left knee swollen and warm but movements normal. Right shoulder also painful. After a period of observation biopsy was performed on knee with report "osteochondritis; no evidence of tuberculosis". X-ray of chest showed prominent hila through due to enlarged bronchial glands. Transferred to medical ward.

EXAMINATION: Thin. Marked pallor. Cervical, axilla and inguinal glands all show enlargement. Systolic mitral murmur. Liver not enlarged. Spleen one inch below costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.8 M., Hb 35%, C.I. 1.0; W.B.C. 4,400. Large lymphocytes 50%, small lymphocytes 23%, neutrophil polymorphonuclears 24%, eosinophil polymorphonuclears 0.5% transitional myelocytes 0.5%, and mononuclears 2%.

PROGRESS: Patient lived three weeks. Glands and spleen continued to enlarge. Liver and testicle became enlarged.

POST MORTUM: Blood stained pleural effusion. Lungs oedematous and subpleural haemorrhages. Heart shows nothing except thrush breast mottling of anaemia. Liver considerably enlarged. Spleen grossly enlarged to umbilicus. Kidneys; infiltration with superadded haemorrhage. Thoracic and abdominal glands enlarged as well as superficial group. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow; majority of cells lymphocytes and their precursors. Hardly any myelocytes. Lymph gland; loss of normal structure. Hyperplasia of lymphocytes; mostly small and some proliferation of larger, pale cells resembling those found in normal germ centres but occurring

In addition to the above lesions practically all cases had alimentary tract haemorrhages from the mucous membrane or subperitoneal petechiae. A number of the cases had abdominal pain, vomiting, constipation or diarrhoea and melaena but in the cases with the intestinal infiltration the history or progress notes did not draw particular attention to the gastro-intestinal tract.

Boikan³ in a review of intestinal lesions in leucosis states that there is no relationship between symptoms arising from the gastro-intestinal tract and the pathological changes present. This is in keeping with the findings of the present series. He points out that any portion of the tract may be involved, either a long area or an isolated portion. The infiltration may be superficial or deep. Abt¹ states that in children intestinal infiltration is more frequent than gastric and may be accompanied by diarrhoea. Saxl² observed two cases of leucosis in childhood where death was attributed to ileus caused by leukaemic infiltration. Jones¹² recorded a case of leucosis in an adult where intestinal infiltration led to perforation and fatal peritonitis.

KIDNEYS

The kidneys had infiltration present in practically all the cases and in many it was visible on naked eye examination. Only two cases examined at autopsy showed no infiltration. In case 7 the bilateral enlargement of kidneys due to infiltration was sufficiently marked to be detected clinically. In a number of cases haematuria was present either before or after admission but it is noteworthy how seldom attention was drawn to the urinary system. No doubt the clinical and biochemical manifestations of the kidney lesions were missed by oversight and by the gravity of other symptoms. One case with testicular pain and swelling during

in a diffuse manner. No multinucleated cells or fibrosis. Eosinophils sufficiently numerous to be noteworthy. Liver; portal tract infiltration of lymphocytes and the paler cells described above. Slight fibrosis, Spleen; Malpighian bodies hyperplastic and well defined. Cells mostly small lymphocytes with a few eosinophils. Kidney; lymphocytic infiltration with haemorrhage. Testicle; gross lymphocytic infiltration in interstitial tissue.

DIAGNOSIS: Lymphadenosis.

CASE 17

M.M., female, aged two years two months. Admitted 16/8/30 with history of scarlet fever four months previous and followed by whooping cough. As she began to get better of latter illness pallor developed. Purpuric spots present for several weeks.

EXAMINATION: Well developed but thin. Marked pallor. Purpuric spots. Slight enlargement of cervical and inguinal glands. Tonsils enlarged but mouth and throat healthy. Liver and spleen moderately enlarged. Other systems, no appreciable disease.

BLOOD COUNT: As patient died few hours after admission count not performed but film showed hypochromic anaemia, poikilocytosis and anisocytosis. Extreme degree of leucocytosis, cells mostly small lymphocytes.

POST MORTUM: Thrush breast myocardium. Petechial of lungs and heart. Liver shows fine white striations. Spleen three times normal size. Kidneys considerably enlarged and a diffuse greyish white appearance. Slight peribronchial and moderate abdominal gland enlargement. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Lymph gland; leukaemic infiltration of lymphocytes. Liver; marked portal tract leukaemic infiltration. Spleen; marked lymphocytic infiltration with Malpighian bodies ill defined. Kidney; gross

leukaemic infiltration. Myocardium; small foci of lymphocytes present.

DIAGNOSIS: Lymphadenosis.

CASE 18

J.L., male, aged two years eleven months. Admitted 26/1/29 with history of lassitude and pallor for three weeks. Epistaxis two days before admission.

EXAMINATION: Well nourished. Marked pallor and purpuric spots. Cervical, axilla and inguinal glands enlarged. Mouth healthy. Liver and spleen each two and a half fingers breadth below costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.3 M., Hb 20%; C.I. 0.8; W.B.C. 3,600. Small lymphocytes 65%, large lymphocytes 26%; neutrophil polymorphonuclears 8% and mononuclears 1%.

PROGRESS: Died one week after admission. Little change in blood count. Oedema developed. Day before death spleen shrunk to half a finger breadth below costal margin.

POST MORTUM: Lungs oedematous and subpleural petechial. Heart has thrush breast appearance. Spleen considerable enlarged. Liver not enlarged. Slight enlargement of thoracic and abdominal glands. Other organs, No appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow almost all of lymphoid series. Large endothelial phagocytes present, Lymph gland; normal architecture obscured by lymphocytic infiltration. Liver; portal tract infiltration of large and small lymphocytes. Spleen; infiltration obscuring Malpighian bodies. Kidney; infiltration present. The predominant cell type in all of the above is a large lymphocyte or lymphoblast.

DIAGNOSIS: Lymphadenosis.

CASE 19

H.M., male, aged seven and a half years. Admitted 27/9/27 with history of abdominal pain and vomiting for three months. Stools dark for past week. Increasing pallor. Glands of neck enlarged in past few days.

EXAMINATION: Well developed and good nutrition. Pallor. Several purpuric spots over body. Bleeding from mouth. Gums spongy and raw. Glands of neck enlarged. Liver enlarged and tender. Spleen one or two finger breadths below costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.2 M., W.B.C. "Very numerous; not countable". Film shows numerous white cells of myeloblastic or lymphoblastic type. Patient died on day of admission.

POST MORTUM: Mouth as above; no necrosis. Lungs with subpleural petechiae. Heart; haemorrhages into myocardium. Liver enlarged nearly to umbilicus and of pale colour. Spleen much enlarged. Kidneys pale and questionable infiltration or haemorrhage. Intestine; bowel contents deeply blood stained and very numerous submucous petechiae. Cervical, thoracic and abdominal glands enlarged and they show haemorrhage into the substance of the glands. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow cellular. The chief cell is a large one with notched nucleus some being deeply notched and they are probably myeloblasts. Liver; diffuse leukaemic infiltration including the portal tracts. Spleen; well preserved. Malpighian bodies but leukaemic infiltration present. Kidneys; leukaemic infiltration of interstitial tissue.

DIAGNOSIS: Leucosis, probably myelosis.

life had leukaemic infiltration of testes at post mortem.

ADRENALS

In but one case was microscopic examination of the adrenal glands carried out. On that occasion, case 7, leukaemic infiltration was marked. It is problematical whether this involvement played a significant part in the clinical picture of the case.

BONES AND JOINTS

Involvement of bones may give rise to pain in the sternum which appears to be due to an active proliferative process in the marrow. Case 7 had this symptom but it appears less frequent as a symptom in childhood. Probably this is not due to decreased prevalence but rather inability of the younger group of cases to make known this symptom. In the long bones there are infiltrations in the subperiosteal regions causing elevation of periosteum and severe pain. Either with or without this type of bone pain one may have marked joint pains. In these cases the pain would appear to be due to haemorrhagic effusions into the joint cavities and associated tissues but it is remarkable how few recorded cases with joint involvement have had post mortem examination of the involved areas.

Radiological examination of the long bones often shows leukaemic changes and may be of diagnostic assistance.

Strauch²² in 1913 was one of the first to emphasize "articular rheumatism" as a presenting picture in acute leucosis in children. Poyton¹⁹ has pointed out that the diagnosis of leucosis with a "rheumatic history" may be extremely difficult since the first sound of the heart in acute leucosis may be so short and sharp as to suggest a mitral stenosis and be followed by a systolic murmur which may be traced to the axilla. Some cases of leucosis may have a marked clinical

CASE 20

C.M., female, aged eleven months. Admitted 24/7/27 with a history of sore mouth, epistaxis, pallor and diarrhoea for one week. Bruises present for one day.

EXAMINATION: Poor development and nutrition. Marked pallor and purpuric spots. Enlargement of cervical, axilla and inguinal glands. Epistaxis. Spongy gums. Throat healthy. Liver and spleen each one and a quarter inch below costal margin. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.9 M., Hb 35%, C.I. 0.9, W.B.C. 243,000. Myelocytes 90%, neutrophil polymorphonuclears 2% and lymphocytes 8%. No nucleated red cells seen.

PROGRESS: Died within two days.

POST MORTUM: Heart; nil except subpericardial haemorrhages. Liver enlarged and pale. Spleen very large. Kidneys; subcapsular haemorrhage in one. Mesenteric glands enlarged and hilar glands slightly enlarged. Other organs, no appreciable disease.

MICROSCOPIC EXAMINATION: Bone marrow is cellular and chiefly myeloblastic. Spleen; massive leukaemic infiltration. Kidney, liver and gland all show slight leukaemic infiltration.

DIAGNOSIS: Myelosis.

CASE 21

W.L., male, aged two years eight months. Admitted 2/8/26 with history of swelling of glands of neck and pains over whole body for nine days. Spots for five days. Feverish and off food for some days and accompanied by diarrhoea with streaks of blood.

EXAMINATION: Nutrition good. Marked pallor. Purpuric rash over whole body. Enlargement of cervical, axilla and inguinal glands. Liver slightly enlarged. Spleen one finger breadth below costal margin.

similarity to malignant endocarditis. On the other hand the resemblance to less acute rheumatism may be seen as in the case of Conybeare where a boy of eight years developed a lymphadenosis which began with a classical picture of Still's disease.

In six cases of the present series there were marked symptoms or signs referable to the long bones and associated joints. One case of lymphadenosis which had been aleukaemic in character was admitted to the surgical ward for pain and swelling of the knee. Diagnosis was uncertain and a biopsy performed with report "osteochondritis; no evidence of tuberculosis". X-ray showed enlargement of hilar shadow, probably enlarged glands. Autopsy established diagnosis of lymphadenosis. Unfortunately the joint was not examined at post mortem but it appears likely that the joint symptoms were part of the leucosis picture.

HEART

Mention has been made of the presence of mitral murmurs. Cardiac symptoms and signs are largely dependent on the severity of the anaemia. Post mortem appearance showed frequent subepicardial or endocardial petechiae and the thrush breast appearance of anaemia was not infrequent. Microscopic examination showed leukaemic infiltration in three cases examined. Wintrobe²⁶ mentions that rupture of the left auricle and of the descending aorta as the result of leukaemic infiltration has been observed.

LUNGS

The presence of superadded infection is frequently seen in leucosis and respiratory infection is particularly common. Post mortem examination frequently revealed subpleural petechiae and bronchopneumonia in a considerable number of cases. Leukaemic infiltration of the lungs was found in three cases.

NERVOUS SYSTEM

Involvement of central nervous system was not observed in any of this series. although in adults it is not infrequent. The acuteness of the disease and the difficulty in detecting the signs of minor neurological involvement probably accounts for the negative findings. In a few cases ophthalmic examination was carried out and retinal haemorrhages were found.

SKIN

No leukaemic infiltration of the skin was found in these cases. However, it does occur in leucosis in childhood but the incidence is less than in adults. Haemorrhages into or beneath the skin was an extremely common feature.

STERNAL PUNCTURE

When one considers the multitude of symptoms and signs which may occur in leucosis it is easy to understand the difficulty in diagnosis in the numerous atypical cases. However, if one realizes that leucosis is not a rare disease and that one may have symptoms referable to any system then many cases will not be missed. In all cases of leucosis a sternal puncture is of interest and in many cases it is of great assistance. The interpretation of the bone marrow findings in children is somewhat more difficult than in adults but studies of Vogel and Bassen²⁴ and also those of Kato¹³ have assisted in determining normal and pathological findings. However, blood dyscrasias, the marrow in leucosis is often one of the simplest to differentiate from normal in view of the gross changes present. One must realize that although this is generally so there are cases of leucosis where portions of the marrow may be relatively normal in appearance. Case 9 is a striking example of this feature. It should be born in mind

that although sternal puncture is usually sufficiently accurate for diagnostic purposes nevertheless it does not give as accurate a picture of the marrow as does a trephine biopsy.

AETIOLOGY

The aetiology of leucosis is obscure. The infective and neoplastic theories both have their adherents. The acute leucosis resemble an infective disease in many ways. However, a chronic leucosis may become acute and a study of both types leads one to believe that they are of the same fundamental pathology. The weight of evidence points to the neoplastic character of the disease. Some observers have been struck by the frequency of infectious diseases preceeding the onset of leucosis but this series does not support this. The recent history of infectious disease was of no greater frequency than would be expected from any other group of admissions to hospital.

The last six cases of this series present an unusual incidence in that they died within a period of twelve months. The previous six cases extended over a period of seven years and the six cases preceeding these, occurred in an interval of twenty months. It is not known whether this apparent epidemic tendency has any significance. In relation to this, mention should be made to a recent observation of Sydenstricker who studied seven cases of acute myelosis in young people from a very limited section in South Georgia. These occurred rapidly one after another and comprised more cases of leucosis than had been seen from the same area in twenty five years.¹⁶

FAMILY HISTORY

The family history and previous history of patient were usually negative. One mother had a history of "pernicious anaemia" and several parents gave a history of "anaemia" but otherwise there was no blood dyscrasia

amongst the parents. In this respect Shipton²¹ describes a case of a boy, aged fifteen years, who died of acute myelosis and one year later the mother died of the same condition. He also reports two other groups of alleged familial leucosis but the evidence appears inconclusive. Jelke¹¹ in 1939 recorded acute leucosis in uniovular twins which is the second time in literature that this has been noted. Kelsey¹⁵ in the same year reported a case of congenital leucosis and in reviewing the literature accepted nine of the cases reported as genuine leucosis and eight of these were myelosis. None of the parents suffered from the disease. Dameshek⁷ recorded chronic lymphadenosis in twin brothers, age fifty-six, who died within a few months of one another. On reviewing the literature and on close clinical and haematological study of many cases of leucosis and familial occurrence Shipton was led to the suggestion that it might be regarded as a disease of low infectivity which attacks individuals with some inherent weakness of endocrine glands controlling the haemopoetic system.

In the present series Case 2 and case 3 are of particular interest, being an example of leucosis in siblings. Case 3 was admitted to hospital at the age of eighteen months. He was the sixth child in a healthy family. From the clinical, haematological and biopsy findings he was considered a lymphadenosis of aleukaemic type. Nine years later the twelfth child, a male, aged two years and three months was admitted to hospital with a history and clinical findings not unlike his brother. In both cases the leucocyte count was normal during most of the period under observation. In these cases lymph glands were slight to moderately enlarged and in neither case was splenomegaly observed. They died within five months of each others age.

Finally, in considering familial incidence mention should be made of case 9 a male, who was a twin. The other twin at time of admission was alive and well.

TREATMENT

The various forms of therapy carried out were legion and no evidence was found of any treatment being of avail although transfusion did, at times, relieve the symptoms due to severe anaemia. An occasional case had short periods of remission. Case 4 improved so much that the child was sent to convalescent home and the original diagnosis of lymphadenosis doubted. This was soon followed by a deterioration and the child was dead within two months of the original admission. An autopsy confirmed the diagnosis.

PROGNOSIS

The prognosis of acute leucosis is invariably hopeless. Nevertheless, a more careful investigation into these cases should teach us much which is at present unknown particularly in the early stages of the disease. It is to be hoped that light on the aetiology and later the prevention or treatment will not be too distant. At present, the chief practical point is to differentiate it from the numerous general and blood diseases which it may mimic.

SUMMARY

1. Thirty cases of acute leucosis in children are presented, twenty of them with post mortem.
2. Death invariably resulted and usually rapidly. Nearly half of the series were dead within one week of admission.
3. The disease is one of early childhood with half the cases occurring under the age of three years.
4. Males were more frequently affected with nineteen cases as compared to eleven females.
5. There is no clinical difference between myelosis and lymphadenosis. In this series the latter type predominated with twenty two cases as compared

Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 3.4 M., Hb 55%; C.I. 0.8; W.B.C. 286,000.

Large and small lymphocytes 94%, neutrophil polymorphonuclears 3%, eosinophil polymorphonuclears 1% and mononuclears 2%.

PROGRESS: Steadily deteriorated. Glands of neck enlarged. Died eleven days after admission. Two days before death W.B.C. 210,000 with lymphocytes 95%.

POST MORTUM: Well developed and nourished. Necrotic stomatitis. Questionable pneumonic consolidation. Petechial haemorrhages in heart and in alimentary tract. Liver and spleen enlarged. Kidneys enlarged and pale with haemorrhages into substance. Mediastinal and mesenteric lymph glands enlarged. Other organs, no appreciable disease.

No microscopic report available.

DIAGNOSIS: Lymphadenosis.

CASE 22

B.M., male, aged two years four months. Admitted 23/9/36 with history of being pale for most of life. Pain in legs, listlessness and anorexia for two weeks.

EXAMINATION: Moderate nutrition. Marked pallor. Enlarged glands in neck and axilla. Mouth and throat healthy. Liver three fingers breadth below costal margin. Spleen not palpable. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.4 M., Hb 35%; C.I. 1.2; W.B.C. 9,400.

Lymphocytes, large and small, 94%, neutrophil polymorphonuclears 4%, monocyte 1%, eosinophil polymorphonuclears 5%, and basophil polymorphonuclears 0.5%. Film shows polychromasia, occasional nucleated red cell and one lymphoblast.

to eight myelosis.

6. Anaemia was an almost constant finding and usually of severe degree.

7. Leucocyte picture was very varying and cases might be leucopenic at one stage and have a leucocytosis at another time. In lymphadenosis a moderate leucocytosis of 15,000 to 30,000 was common. The myelosis cases tended to have more marked leucocytosis.

8. A slight to moderate enlargement of all groups of lymph glands was usual, but not invariably so.

9. Splenic enlargement was nearly always present.

10. Liver enlargement was very common.

11. Ulcerative stomatitis was found in five cases.

12. Three cases had naked eye infiltration of the intestinal tract.

13. Kidney infiltration was almost always found.

14. Less common infiltration was noted in heart, lungs, adrenals and testes. No skin or nervous system leukaemic infiltration was found.

15. Involvement of bones and joints was not uncommon and a number of cases presented themselves as "rheumatism".

16. Diagnosis may be difficult even with the aid of complete blood examination but sternal puncture may be of great diagnostic assistance.

17. Two of the cases were siblings, both with leucosis of atypical character.

18. There was no evidence of therapy having any appreciable affect in altering the inevitable fatal outcome.

PROGRESS: Child was taken home after one week in hospital.

Condition deteriorating. White count never over 12,000.

DIAGNOSIS: Lymphadenosis.

CASE 23

J.S., male, aged three years three months. Admitted 15/1/35 with history of being "off colour" following a cold one month ago. Fevered and drowsy. No vomiting. Sent to hospital as suspected tuberculous meningitis.

EXAMINATION: Good development and nutrition. Marked pallor. Throat healthy. Liver not enlarged. Spleen palpable. Lumbar puncture negative. Other systems, no appreciable disease.

BLOOD COUNT: R.B.C. 1.6 M., Hb 22%; C.I. 0.7; W.B.C. 360,000. Myelocytes 92%, degenerate cells 4%, neutrophil polymorphonuclears 3% and lymphocytes 1%.

PROGRESS: Patient deteriorated rapidly and taken home to die.

DIAGNOSIS: Myelosis.

CASE 24

K.M., female, aged two years three months. Admitted 19/3/32 with history of listlessness and pallor for six weeks. Painful limbs and bruising for two weeks. Haematuria, unaccompanied by other urinary symptoms, for one week.

EXAMINATION: Good development and nutrition. Marked pallor. Few fading purpuric spots. Cervical axilla and inguinal glands enlarged. Tonsils enlarged, petechiae on one. Spleen enlarged nearly to umbilicus. Liver not enlarged. Tenderness over femur, humerus and tibia. Urine shows albumin and numerous red cells. Other systems, no appreciable disease.

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